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Emergence of Daptomycin Resistance in *Enterococcus faecium* during Daptomycin Therapy

Daptomycin is a cyclic lipopeptide antibiotic that has been available in the United States since September 2003. We report a clinical and bacteriological failure of daptomycin therapy for enterococcal bacteremia. Briefly, a 22-year-old man with Hodgkin's lymphoma, subsequent acute myelogenous leukemia, and nonseminomatous testicular carcinoma developed neutropenic fever during chemotherapy in 2004. A urine culture at hospital admission yielded 50,000 to 100,000 CFU of *Enterococcus faecium*/ml that were resistant to vancomycin (VRE) but susceptible to daptomycin (MIC = 2 μg/ml) and doxycycline. The patient initially received doxycycline, cefepime, metronidazole, and vancomycin. Two days later, a urine culture grew <10,000 CFU of VRE/ml. Computed tomography of the abdomen revealed bilateral wedge-shaped renal hypodensities compatible with a diagnosis of focal pyelonephritis. All blood cultures obtained during early hospitalization were negative, and on hospital day (HD) 8 the patient's urine culture was negative. Due to persistent fever, daptomycin (6 mg/kg of body weight/day) was used in place of doxycycline and vancomycin beginning on HD 9 and continuing until HD 26, for 17 days of therapy. When chemotherapy was again initiated, the fever returned, and blood cultures at that time grew *Escherichia coli*, for which meropenem was initiated. The patient continued to be febrile, and a blood culture revealed VRE. Susceptibility testing performed by the broth microdilution method with calcium-supplemented Mueller-Hinton broth and by the disk diffusion procedure (5, 6) indicated a daptomycin MIC of greater than 32 μg/ml and a reduced disk diffusion zone diameter (Table 1). While the daptomycin MIC reflected resistance, the zone of inhibition was within the range indicative of susceptibility (i.e., ≥11 mm) by the recently published breakpoints (3). Daptomycin was discontinued and linezolid was initiated at 600 mg intravenously twice daily. The fever persisted, and daptomycin-resistant VRE again grew from two blood cultures obtained 5 days after linezolid was initiated. Linezolid was continued with the addition of doxycycline, and the catheter was removed. The fever abated, and all further blood cultures were negative. Pulsed-field gel electrophoresis of SmaI digests of chromosomal DNA of the four VRE isolates indicated that they were highly related.

Daptomycin is a new agent for treating serious methicillin-resistant *Staphylococcus aureus* (MRSA) and enterococcal infections (1, 2). Its value has been due in part to the fact that resistance of MRSA and VRE to linezolid has already been encountered, and quinupristin-dalfopristin resistance of VRE has been widely reported (7, 8, 9). A previous examination of a collection of unrelated VRE from several geographic areas of the United States did not reveal any isolates with daptomycin MICs that exceeded 8 μg/ml (4). This appears to represent the first description of a clinical and bacteriological failure of an invasive VRE infection due to the emergence of high-level daptomycin resistance during therapy. However, a recent report has illustrated the emergence of resistance in MRSA isolates during daptomycin therapy (K. Rezai, J. P. Quinn, R. Hayes, K. Lolans, R. A. Weinstein, and M. K. Hayden, Abstr. 44th Intersci. Conf. Antimicrob. Agents Chemother., abstr. K-97a, 2004). Clinicians and microbiologists should be aware of the possibility of the emergence of daptomycin resistance and closely monitor the susceptibilities of subsequent isolates that might be recovered during therapy. However, the present breakpoints for the disk diffusion test do not appear to be reliable for the detection of resistance.

TABLE 1. MICs of selected antibiotics against pre- and postdaptomycin therapy VRE isolates

Isolate no. and source	MIC (μg/ml) for:					
	Ampicillin	Vancomycin	Daptomycin[a]	Linezolid	Quinupristin-dalfopristin	Doxycycline
1, urine	>128	>128	2	2	0.5	≤0.25
1, blood	>128	>128	>32	2	0.5	≤0.25
2, blood	>128	>128	32	2	0.5	≤0.25
3, blood	>128	>128	32	2	0.5	≤0.25

[a] Daptomycin zones of inhibition were 19 mm for the urine isolate and 13 mm for the blood isolates.

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